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TITLE: Fusions of Breast Carcinoma and Dendritic Cells as a Vaccine for the
Treatment of Metastatic Breast Cancer

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**Vaccination of Patients with Metastatic Breast Cancer with Dendritic
Cell/Breast Cancer Fusions in Conjunction with IL-12
Department of Defense Grant # DAMD17-03-1-0487
Annual *FINAL* Report for the Period 07/01/2009 - 06/30/2010**

**David Avigan, MD
Baldev Vasir, PhD
Donald Kufe, MD**

Introduction

The overall objective of the project is to study the safety, immunologic response, and clinical effect of vaccination with dendritic cell (DC)/breast cancer fusions administered in conjunction with IL-12 in patients with metastatic breast cancer. Fusion of autologous tumor cells with DCs presents the entire repertoire of tumor antigens, including those yet to be identified, in the context of DC-mediated costimulation. The fusion cell vaccine allows for induction of helper T and CTL responses by class II presentation of exogenous protein and class I presentation of newly synthesized endogenous protein. Vaccination with fusion cells has eradicated established tumor in diverse animal models. In human MUC1 transgenic mice, vaccination with fusion cells reverses immunological unresponsiveness to MUC1 and results in the rejection of MUC1-positive tumors. Preclinical studies with patient-derived breast cancer cells and DCs have also demonstrated that fusion cells induce tumor-specific CTL responses and lysis of autologous tumor cells. In clinical studies, vaccination with fusion cells was well tolerated, induced immunologic responses in a majority of patients, and results in disease regression in subset of patients. We postulated that administration of the vaccine in conjunction with IL-12 would further enhance vaccine response by promoting T cell activation.

In the first 3 years of the grant, we examined DC/breast carcinoma fusions with respect to their phenotypic characteristics as antigen presenting cells and their capacity to stimulate anti-tumor immunity. We demonstrated that DC/breast carcinoma fusions strongly express costimulatory, adhesion, and maturation markers as well as the stimulatory cytokines, IL-12 and IFN γ . In addition, fusion cells expressed CCR7 necessary for the migration of cells to sites of T cell traffic in the draining lymph nodes. In concert with these findings, fusions generated with immature and mature DCs potentially stimulated CTL mediated lysis of autologous tumor targets. In year 4 of the grant, we examined the T cell response to DC/breast carcinoma fusions with respect to the presence of activated and regulatory T cells. We demonstrated that DC/breast carcinoma fusions stimulate a mixed population of cells consisting of CD4/CD25/CD69 and CD4/CD25/Foxp3 $^{+}$ cells. The increased presence of regulatory cells was thought to potentially inhibit the in vivo efficacy of the fusion cell vaccine. As such, we have examined several strategies to bias the fusion-mediated T cell

response towards activated cells. We have found that addition of IL-12, TLR7/8 agonists, CPG ODN, or IL-18 increase the relative presence of activated as compared to regulatory cells. Importantly, we have also found that DC/breast carcinoma fusion-induced activation of autologous T cells and then stimulation with anti-CD3/CD28 results in a marked expansion of anti-tumor effector cells.

Body

Our clinical protocol had received approval by the FDA, NCI/CTEP (distributor of IL-12) and Dana-Farber/Harvard Cancer Center. We had also met the requirements as outlined in the DOD review process. However, during the protracted period of review, the availability of IL-12 was suspended for recertification, which significantly delayed the initiation of the clinical trial. We worked closely with Drs. Zweibel and Streicher at CTEP who have assumed control of the IL-12 stocks and have now completed the requisite potency testing for their release.

In the past year, we have been working with our DOD reviewer, Suzanne E. Dolney, to finalize DOD approval so that we can initiate the study. Our correspondence is summarized below:

1. Request for further information from DOD issued 3.4.09
2. Responses to additional requests sent to DOD 3.5.09
3. DOD issued a protocol evaluation form on 3.16.09 allowing the protocol and consent to be submitted back to the IRB for final approval
4. On 5.15.09, the DOD provided the contact person for submitting the study's continuing review and approval
5. On 5.18.09, Continuing Review and approval was submitted to the DOD
6. On 6.16.09, the latest IRB approved version of the protocol and consent was sent to the DOD for review
7. On 6.23.09, the DOD requested CV information and the IRB correspondence for the latest version of the protocol and consent.
8. On 6.23.09, the requested CV information was sent to DOD
9. On 7.1.09, requested IRB correspondence for the latest version of the protocol and consent was sent
10. On 7.16.09, further changes were made to the protocol and consent
11. On 7.28.09, the NCI approval for the latest version of the protocol and consent was sent
12. On 8.5.09, the DOD issued Initial Approval for Protocol, "Vaccination of Patients With Breast Cancer With Dendritic Cell/Tumor Fusions and IL-12," Submitted by Donald W. Kufe, M.D., Dana-Farber Cancer Institute, Boston, MA, and David Avigan, MD, Beth Israel Deaconess Medical Center, Boston, MA, in Support of Proposal, "Fusions of Breast Carcinoma and Dendritic Cells as a Vaccine for the Treatment of Metastatic Breast Cancer," BB IND No. 8184, NCI Protocol No. 6040, DFCI Protocol No. 03-

Preparation for Clinical Trial

During the last quarters, the protocol was activated after completion of a lengthy review process by the FDA, IRB, and DOD as outlined in our correspondence above. Following completion of this review, we initiated the process of patient recruitment.

In this phase I/II clinical trial, patients with metastatic breast cancer undergo vaccination with DC/tumor fusions administered in conjunction with rhIL-12. An initial cohort of patients are treated with the DC/tumor fusions alone. In the subsequent cohort, fusion cells will be administered with rhIL-12 given subcutaneously at the time of vaccine administration and on days 3 and 5. Measures of tumor specific cellular and humoral immunity will be obtained at serial time points following vaccination. Time to disease progression and RECIST measurable disease response will be followed as a secondary endpoint

Details of Patients recruited for the period (September 2009-June 2010)

An initial patient was a woman with metastatic breast cancer and 2 prior treatment regimens for metastatic disease, who had a pleural effusion as a site of accessible tumor for vaccine production. Unfortunately, during the period of protocol assessment, she experienced disease progression requiring other therapy and was unable to participate in the study.

An additional 4 patients underwent evaluation for study participation.

Patient KB is a 39 year old woman, who was diagnosed with breast cancer in 1999 and presented with metastatic disease in 2003. She is followed at the Dana-Farber Cancer Institute, and was receiving chemotherapy for metastatic disease. She was seen by our vaccine group on 3/23/10 to discuss the clinical trial. She was given a copy of the consent form. She chose not to take part in the study at that time. She recently contacted the study team expressing interest in taking part in the study and will be re-assessed for participation in the study.

Patient KO is a 61 year old woman, who has been followed at the Beth Israel Deaconess Medical Center for metastatic breast cancer since 2005. She has involvement of bone and bone marrow, the latter of which is a potential site of tumor acquisition. She expressed interest in pursuing the study and was seen to discuss the study.

Patient RF is a woman with metastatic breast cancer currently being followed at the Dana-Farber Cancer Institute. She has previously banked tumor cells from a

pleural effusion with 1×10^7 cells cryopreserved. We received approval from the FDA to use tumor cells that have been harvested in a previous Dana-Farber/Harvard Cancer Center trial for clinical use in cancer vaccine studies. She is currently receiving chemotherapy at the Dana-Farber Cancer Institute and was going to going to contact the study team if she chooses to take part in the study.

Patient ES is a woman with metastatic breast cancer who was referred from an outside center and was scheduled to be evaluated for further protocol discussion, and assessment. She lives out of state and was sent the consent form to review. She was going to discuss the study with her local oncologist and contact us if she is interested in being evaluated for the study.

Active recruitment for the study was underway.

Temporary Suspension of the protocol

On 06/18/2010, the protocol was temporarily closed to accrual in response to an action letter from CTEP requesting a hold on the protocol and modifications to the protocol and consent form based on a new risk profile for IL-12 (effective 06/01/10). An amended protocol and consent form was submitted to the IRB on 06/18/2010. The FDA was notified on 06/11/2010. The amended protocol was reopened to accrual on 07/16/2010. Patients recruited to the study after this date form the basis of a quarterly report for the period 07/01/2010 – 09/30/2010

Attached to this report are the active human use documents and approvals.

Continuing Review: Notification of IRB Approval/Activation

DFCI Legacy #: 03-221

Date: 04/16/2010

To: David Avigan, MD

From: OHRS

Title of Protocol: Vaccination of Patients with Breast Cancer with Dendritic Cell/Tumor Fusions and IL-12
Version/Number: NCI #6040; Version 7: 07/21/2009
IRB Continuing Review #: 7
IRB Review Type: Expedited - (8)(b)
IRB Approval Date: 04/06/2010
IRB Expiration Date: 04/06/2011

This Project has been reviewed and approved by the DFCI IRB, Assurance # FWA00001121. During the review of this Project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for securing and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

Notes: Approved for one year Expedited per 45CFR 46.110(b); Category 8b.

As Principal Investigator you are responsible for the following:

1. Submission in writing of any and all changes to this project (e.g., protocol, recruitment materials, consent form, study completion, etc.) to the IRB for review and approval prior to initiation of the change(s), except where necessary to eliminate apparent immediate hazards to the subject(s). Changes made to eliminate apparent immediate hazards to subjects must be reported to the IRB within 24 hours.
2. Submission in writing of any and all adverse event(s) that occur during the course of this project in accordance with the IRB's policy on adverse event reporting.
3. Submission in writing of any and all unanticipated problems involving risks to subjects or others.
4. Use of only IRB approved copies of the consent form(s), questionnaire(s), letter(s), advertisement(s), etc. in your research. Do not use expired consent forms.
5. Informing all physicians listed on the project of changes, adverse events, and unanticipated problems.

The IRB can and will terminate projects that are not in compliance with these requirements. Direct questions, correspondence and forms (e.g., continuing reviews, amendments, adverse events, safety reports) to OHRS Office, 617-632-3029.

cc:

David E Avigan, MD, East Campus Kirstein D3A83



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